REMARKS

Reconsideration of this application is respectfully requested. Claims 41-44 have been added. Support for these claim amendments is found at, for example, page 1, lines 12-19, and page 5, lines 16-27, of the specification. Claims 20-44 are pending and at issue.

Obviousness-Type Double Patenting

Claims 20-40 have been provisionally rejected for obviousness-type double patenting over claims 36-46 of U.S. Patent Application No. 10/468,685, claims 20-34 of U.S. Patent Application No. 10/644,587, and claims 20 and 22-37 of U.S. Patent Application No. 10/644,588, in view of Applicant's allegedly admitted prior art. Applicant respectfully requests that these provisional rejections be held in abeyance because none of the patent applications containing the conflicting claims have been allowed or issued as patents.

Obviousness Rejection

Claims 20-40 have been rejected under 35 U.S.C. §103(a) as obvious over U.S. Patent No. 4,943,590 ("Boegesoe") in view of the present specification. The Examiner cites Boegesoe as disclosing a method of treating depression using escitalopram, and cites the present specification as disclosing that clinical studies on depression show that non-response or resistance to selective serotonin reuptake inhibitors (SSRIs) is substantial. From this, the Examiner concludes that it would have been obvious for one of ordinary skill to treat depression in a patient who failed to respond to a non-escitalopram SSRI by administering escitalopram because, in the Examiner's view, Boegesoe discloses "escitalopram as being the more effective enantiomer at inhibiting serotonin uptake." Office Action, p. 6.

This rejection is respectfully traversed, and reconsideration is requested.

A *prima facie* case of obviousness has not been established

Contrary to the Examiner's contention, one of ordinary skill in the art would not have been motivated to administer escitalopram for the treatment of depression in patients who have failed to respond to treatment with an initial non-escitalopram SSRI, as called for in the pending claims. In these patients, administration of an SSRI (other than escitalopram) has been shown to be ineffective in treating their depression. Given the failure of a first SSRI to produce an effective response in these patients, one of ordinary skill in the art would not have reasonably expected them to then respond to another member of the exact same drug class. Rather, any reasonable expectation of success associated with SSRIs would be necessarily diminished in this population.

In the March 29, 2007 Office Action, the Examiner argues that one of ordinary skill in the art would, after failing to effectively treat depression with a first SSRI, "administer another SSRI." This infers that a skilled artisan would correlate the failure of the first SSRI to its chemical structure rather than its mechanism of action. Applicants respectfully submit that as of May 2001, the effective filing date of the present application, one of ordinary skill in the art would not assume that the failure was solely due to the chemical structure of the SSRI. Rather, after failure with a first treatment with a SSRI, one of ordinary skill in the art would select a different therapy, which if it included an antidepressant, would have a different core structure and different mechanism of action. This is particularly so in view of the numerous other treatment options available for patients with depression, such as psychotherapy, monoamine oxidase inhibitors, tricyclic antidepressants, noradrenaline reuptake inhibitors, and other atypical agents such as nefazodone and buproprion. Given this wide range of options, one of ordinary skill in the art would not have had the motivation to use a second SSRI to treat depressed patients after a first SSRI failed. In fact, one of ordinary skill would have been discouraged by the patients' initial failure to respond to SSRI treatment, and would have more likely turned to a different drug class or method for treatment.

Even assuming, *arguendo,* one of ordinary skill would have expected this treatment-resistant patient population to successfully respond to a second SSRI, this is merely a broad generalization and would have provided no reasonable expectation of success with respect to the efficacy of escitalopram in particular. Boegesoe does not cure this problem because one of ordinary skill in the art reading Boegesoe would understand that it generically discloses the use of escitalopram for the treatment of depressed patients, but provides no guidance as to whether or not this compound would be effective in the SSRI-resistant patients called for in the pending claims. The present specification discloses that a substantial percentage of patients do not respond to certain SSRIs even though SSRIs are a primary therapeutic option for the treatment of depression. *See* specification at p. 1, lines 12-19. Hence, even if one of ordinary skill in the art reasonably expected (albeit to a diminished degree) that a second SSRI would be effective in treating depression in non-responsive patients, the disclosure in Boegesoe would not have provided the requisite motivation to single out escitalopram from the several other known SSRIs as the SSRI of choice.

Unexpected results

Additionally, even assuming, *arguendo,* that the cited reference supports an obviousness rejection, evidence of unexpected results can rebut a *prima facie* case of obviousness. *See* MPEP §716.02(a). Applicants have surprisingly found that escitalopram is effective in patients who have failed to respond to initial treatment with a SSRI other than escitalopram. This is shown by a clinical study reported in the attached poster by D.L. Zimbroff et al. (presented at CINP2004) and abstract of the same (*Int. J. Neuropsychopharm.* 7(S1):S348, P02.164 (June 2004)). In this study, depressed patients (MADRS $\geq$ 22) received 8 weeks lead-in treatment with citalopram, fluoxetine, paroxetine, or sertraline (all of which are SSRIs). Patients having an MADRS score of at least 13 after the lead-in treatment were categorized as "SSRI non-responders" and received an additional 8 weeks treatment with escitalopram (10-20 mg/day). Remission rates for patients switched from sertraline, fluoxetine, citalopram, and paroxetine were 56%, 38%, 37% and 34%, respectively. *See* the Zimbroff poster (left column, under the heading "Abstract" and subheading "Results"); *see also*

the Zimbroff abstract which reports remission rates of 65% (sertraline), 44% (fluoxetine), 42% (citalopram), and 42% (paroxetine). The authors conclude that "[t]hese data confirm that escitalopram can be effective in patients failing therapy with citalopram and other SSRIs."

The efficacy of escitalopram (10-20 mg/day) in patients who failed to respond to treatment with citalopram (20-60 mg/day) is especially surprising since citalopram is a racemate, containing equal parts of the R and S enantiomers. Escitalopram is the S-enantiomer. Thus, if all of the therapeutic effect of citalopram resides in escitalopram, the therapeutic effect of one dose of escitalopram should be the same as two doses of citalopram. A skilled artisan would have expected that subsequent treatment with 10-20 mg escitalopram would at best have the same therapeutic effect as the 20-60 mg citalopram treatment (which contains 10-30 mg/day escitalopram and 10-30 mg/day R-citalopram). Accordingly, after a patient failed to respond to treatment with citalopram (20-60 mg), one of ordinary skill in the art would not have been motivated to treat the patient with escitalopram (10-20 mg). The data, however, show surprisingly that in a comparison of 10-20 mg of escitalopram vs. 20-60 mg of citalopram, the therapeutic effect was not the same. Escitalopram was surprisingly more effective alone than when administered with the R-enantiomer as part of the racemate. For these reasons in addition to those above, claims 41-44 are non-obvious over Boegesoe.

In summary, claims 20-40 are not obvious because one of ordinary skill in the art would not have been motivated to use escitalopram to treat depression in a patient after a first member of this same class of drugs had proven unsuccessful, particularly because several other types of treatment options were known to those of skill in the art and would have therefore been more reasonably selected. Furthermore, the successful treatment of depressed patients who failed to respond to treatment with four other SSRIs (citalopram, fluoxetine, paroxetine, and sertraline) is surprising in view of the initial failure with an SSRI. Finally, the successful treatment of patients who failed to respond to initial treatment with citalopram is particularly surprising given that citalopram contains equal parts of escitalopram and R-citalopram.

For the foregoing reasons, the presently claimed invention is non-obvious over the cited prior art. Accordingly, applicants respectfully request that this rejection be withdrawn.

Information Disclosure Statement

Submitted herewith is an Information Disclosure Statement, which cites the above-mentioned Zimbroff poster and abstract as well as an abstract of Thase et al. (*J. Clin. Psychiatry*, 2001:62, 683-687) and a poster by Burke et al. (Presented at the 42nd Annual Meeting of the American College of Neuropsychopharmacology, Dec. 7-11, 2003, San Juan, Puerto Rico). The Thase and Burke references are cited in the Zimbroff poster. Applicants respectfully submit that none of these references are prior art to the present application. The present application claims priority and is entitled to the filing date of Danish application no. PA 2001 00684 filed May 1, 2001, which is prior to the publication date of any of these references. *See* page 1, lines 12-19, page 2, lines 9-16, and page 5, lines 10-14, of the Danish priority document.

Conclusion

In view of the above amendments and remarks, it is respectfully requested that the application be reconsidered and that all pending claims be allowed and the case passed to issue.

If there are any other issues remaining, which the Examiner believes could be resolved through either a Supplemental Response or an Examiner's Amendment, the Examiner is respectfully requested to contact the undersigned at the telephone number indicated below.

Dated: October 1, 2007

Respectfully submitted,

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P02.164

Escitalopram Treatment of SSRI Non-Responders Can Lead to Remission in Patients Who Fail Initial SSRI Therapy

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Abstract

Introduction. In routine practice, patients failing one SSRI are sometimes switched to another SSRI. Escitalopram has been shown to be effective in patients who failed to respond to citalopram.

Methods. Depressed outpatients (18-65 years; MADRS ≥ 22) were randomized to receive 8 weeks lead-in treatment with open-label citalopram (20-60 mg/day, N = 131), fluoxetine (20-80 mg/day; N = 129), paroxetine (20-50 mg/day; N = 128), or sertraline (50-200 mg/day; N = 127). Patients completing lead-in treatment with a MADRS score of at least 13 were eligible for 8 weeks open-label escitalopram (10-20 mg/day) in a follow-on trial. Remission was defined as MADRS ≤ 10. LOCF results are presented.

Results. In the lead-in trial, the proportion of patients with MADRS ≤ 12 at endpoint was similar for citalopram and sertraline (56% vs 55%) and somewhat lower for paroxetine and fluoxetine (50% and 43%, respectively). Similar results were observed for the proportion of patients with ≥ 50% reduction in MADRS scores (citalopram 61%, sertraline 61%, paroxetine 51%, fluoxetine 50%). A total of 137 SSRI non-responders completing lead-in treatment were switched to escitalopram, of whom 136 were evaluated for efficacy; 80% completed escitalopram treatment. Following switch to escitalopram, remission rates were highest for patients switched from sertraline (56%), followed by patients switched from fluoxetine (38%), citalopram (37%), and paroxetine (34%). Escitalopram was well tolerated, with 6.6% discontinuation due to adverse events.

Conclusion: These data confirm that escitalopram can be effective in patients failing therapy with citalopram and other SSRIs.

Introduction

Selective serotonin reuptake inhibitors (SSRIs) are the most widely used class of antidepressants, however, a substantial proportion of patients (20% to 40%) may fail to respond adequately to an initial trial with an SSRI.[1] Published reports of switching SSRI non-responders to a second SSRI have shown that there is value in this treatment strategy.[2] Escitalopram has been shown to be effective in patients who failed to respond to citalopram.[3] This study evaluated the efficacy of escitalopram in patients who did not respond to 8 weeks of treatment with adequate doses of other SSRIs.

Methods

Study Design

- Depressed outpatients (MADRS ≥ 22) age 18-65 years randomized to 8 weeks open-label treatment with flexible doses of one of four SSRIs:
  - citalopram 20-60 mg/day
  - fluoxetine 20-80 mg/day
  - paroxetine 20-50 mg/day
  - sertraline 50-200 mg/day
- Patients with MADRS ≥ 13 after 8 weeks were eligible to receive 8 weeks open-label treatment with escitalopram (10-20 mg/day).
- Switch to open-label escitalopram occurred within 24 hours of completing initial SSRI treatment.
  - escitalopram 10 mg/day for first week
  - escitalopram 10-20 mg/day thereafter

Patient Populations

- Safety population: Safety analyses were performed on all patients who received at least one dose of open-label escitalopram treatment.
- Intent-to treat (ITT) population: Efficacy analyses were performed on all patients in the safety population who had at least one post-baseline MADRS assessment.

Efficacy Measures

- Primary measure: Montgomery-Asberg Depression Rating Scale (MADRS)
- Response defined as ≥ 50% decrease in MADRS total score from the start of lead-in treatment.
- Remission defined as MADRS total score ≤ 10.
- Results are presented using last observation carried forward (LOCF) analysis.

Results

Lead-in Treatment

Table 1. Characteristics of Patients Randomized to Open-Label Treatment with Citalopram, Fluoxetine, Paroxetine, or Sertraline

	Citalopram (N = 131)	Fluoxetine (N = 129)	Paroxetine (N = 128)	Sertraline (N = 127)
Age (mean years)	40	40	39	40
Gender (% female)	70%	61%	70%	69%
% Completed	75.6%	70.5%	75.0%	78.7%
% Discontinued Due to Adverse Events	13.7%	16.3%	15.6%	11.8%
Overall Mean Daily Dose (mg/day)	32.7	33.1	25.1	95.0
MADRS Score (mean ± SD)	30.4 ± 4.5	30.7 ± 4.5	30.1 ± 4.4	30.5 ± 4.4

Escitalopram Treatment

- Of patients completing 8 weeks lead-in SSRI treatment, 139 had MADRS scores ≥ 13 and were eligible for follow-on escitalopram treatment. Of these, 137 patients had at least one dose of open-label escitalopram, and composed the safety population. The ITT population consisted of 136 patients (Table 2).

Table 2. Characteristics of SSRI Non-Responders Switched to Escitalopram

	Escitalopram (N = 136)
Age (mean years)	41
Gender (% female)	65%
MADRS Score (mean ± SD)	22.2 ± 6.2
Lead-in Treatment, n (%)	
Citalopram	30 (22%)
Fluoxetine	42 (31%)
Paroxetine	32 (24%)
Sertraline	32 (24%)

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June 20-24, 2004 | Paris, France

- Treatment with escitalopram (mean daily dose = 15.8 mg/day) led to continued improvement in symptoms of depression. Remission (Figure 1), response (Figure 2), and mean change in MADRS score (Figure 3) during escitalopram treatment are presented based on lead-in treatment and for the total population.

Figure 1. Remission Rates (MADRS ≤ 10) after 8 Weeks Open-Label Treatment with Escitalopram (ITT, LOCF)

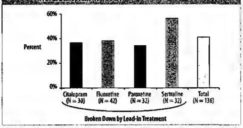


Figure 2. Response Rates (≥ 50% Improvement in MADRS) after 8 Weeks Open-Label Treatment with Escitalopram (ITT, LOCF)

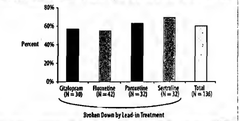
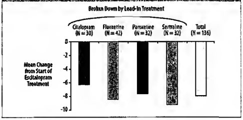


Figure 3. Mean Change in MADRS Scores after 8 Weeks Open-Label Treatment with Escitalopram (ITT, LOCF)



- Among all patients treated with escitalopram, headache was the only adverse event reported by > 10% following switch from another SSRI (Table 3). Fewer than 7% of patients switched from another SSRI to escitalopram discontinued treatment due to adverse events (Table 4).

Table 3. Adverse Events in Patients Switched to Escitalopram

	Escitalopram (N = 137)
Headache	14.6%
Back Pain	9.5%
Diarrhea	7.3%
Fatigue	7.3%
Inflicted Injury	5.8%
Upper Respiratory Tract Infection	5.8%
Nausea	5.8%
Sweating Increased	5.1%

Table 4. Reasons for Premature Discontinuation

	Escitalopram (N = 137)
Withdrawn for Any Reason	19.7%
Adverse Event	6.6%
Protocol Violation	4.4%
Lost to Follow-up	3.6%
Insufficient Therapeutic Response	2.9%
Withdrawal of Consent	2.2%

Conclusions

- SSRI non-responders can be quickly and safely switched to escitalopram, with a reasonable expectation of therapeutic benefit.
- Treatment with escitalopram 10-20 mg/day improves symptoms of depression among patients who did not respond to an initial course of treatment with another SSRI.
- A substantial proportion of patients who fail to respond to one SSRI will respond to escitalopram and achieve remission from depression.
- A rapid switch (within one day) from another SSRI to escitalopram is generally well tolerated, with low rates of discontinuation due to adverse events.

References

1. Sackeim HA. The definition and meaning of treatment-resistant depression. *J Clin Psychiatry* 2001;62(Suppl 16):10-17.
2. Thase ME, Feighner JP, Lydiard RB. Citalopram treatment of fluoxetine nonresponders. *J Clin Psychiatry*. 2001;62:683-687.
3. Burke WJ, Bose A, Wang J, et al. Switching depressed patients from citalopram to escitalopram is well tolerated and effective. Presented at the 42nd Annual Meeting of the American College of Neuropsychopharmacology. December 7-11, 2003, San Juan, Puerto Rico.

concentration at baseline did not differ between the group of depressed patients and healthy controls.

Conclusion: Our study corroborates the evolving concept that antidepressants affect various components of the HPA system with the net result of a reduction in its activity. In addition, we found CSF CRH and CSF somatostatin concentrations to be better reflections of age than of depression and, finally, that during aging and during depression the HPA system changes in similar directions.

P02.163 ASSOCIATION BETWEEN ANTIDEPRESSANT RESPONSE OF MILNACIPRAN AND PLASMA CONCENTRATIONS OF MILNACIPRAN IN JAPANESE PATIENTS WITH MAJOR DEPRESSIVE DISORDER

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Statement of the study: The three preliminary studies did not show the correlation between the plasma concentrations of milnacipran and the antidepressant response in major depressive patients (Retz et al.,1995, Higuchi et al., 2003). The purpose of this study was to clarify the relationship between the plasma concentrations of milnacipran and the antidepressant response in more subjects compared to our previous report.

Methods: A total of 96 Japanese patients meeting DSM-IV criteria for major depressive disorder who scored >20 points on the Montgomery-Åsberg Depression Rating Scale (MADRS) were included. All patients provided written informed consent to participate. Patients received milnacipran in two equally divided doses in after dinner and at bedtime for 6 weeks. The daily dose was 50mg for the first week and 100mg in the remaining 5 weeks. Depressive symptoms were evaluated by the MADRS before treatment and at 1, 2, 4 and 6 weeks after the beginning of this study. A clinical response was defined as a 50% or greater decrease in the baseline MADRS score at the end of this study. A clinical remission was defined as the final MADRS score <10 points.

Summary of results: This report is based on the data of 80 patients (28 male, 52 female; mean age±S.D. = 51.5±12.1). Fifty patients were responders and 43 patients were remitters. The plasma concentrations were 89.0±34.9 and 92.3±45.1 ng/ml (mean±S.D.) in responders and in non-responders, respectively, and there was no significant difference (p=0.72). The plasma concentration of remitters was 91.8±36.0 ng/ml, neither was significant difference between remitters and non-responders (p= 0.95).

Conclusion: There was no significant relationship between the plasma concentrations of milnacipran and the antidepressant response in Japanese major depressive patients.

Hisashi Higuchi, Keizo Yoshida, Hitoshi Takahashi, Shingo Naito, Mitsuhiro Kamata, Kenichi Ito, Kazuhiro Sato, Kei Tsukamoto, Tetsuo Shimizu, Mamoru Nakanishi, Yasuo Hishikawa (2003). Milnacipran plasma levels and antidepressant response in Japanese major depressive paticots Human Psychopharmacology: Clinical and Experimental 18: 255–259.

Retz W, Becker T, Sehmidtke A, Riedener P, Beckmann H (1995). Multiple and single dose pharmacokinetics of milnacipran in major depressive patients (abstract). European Neuropsychopharmacology Special Issue: 296–297.

P02.164 ESCITALOPRAM TREATMENT OF SSRI NON-RESPONDERS CAN LEAD TO REMISSION IN PATIENTS WHO FAIL INITIAL SSRI THERAPY

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Statement of the study: It may be desirable to switch patients failing one SSRI to another SSRI. Escitalopram has been shown to be effective in patients who failed to respond to citalopram.

Methods: Depressed outpatients (18–65 years; MADRS≥22) were randomized to receive 8 weeks lead-in treatment with open-label citalopram (20–60 mg/day; N=129), sertraline (50–200 mg/day; N=125), paroxetine (20–50 mg/day; N=125), or fluoxetine (20–80 mg/day; N=128). Non-responders (MADRS>12) were eligible for 8 weeks open-label escitalopram (10–20 mg/day) in a follow-on trial. Remission was defined as MADRS≤10. LOCF results are presented.

Summary of results: In the lead-in trial, the proportion of patients with MADRS≤12 (responders) was similar for citalopram and sertraline(56% vs. 55%)and somewhat lower for paroxetine and fluoxetine(50% and 43%, respectively). Similar results were observed for proportion of patients with ≥50% reduction in MADRS scores: (citalopram 61%, sertraline 61%, paroxetine 51%, fluoxetine 50%). A total of 137 (of 248) SSRI non-responders switched to escitalopram, of whom 80% completed treatment. Following switch to escitalopram, remission rates were highest for patients switched from sertraline(65%), followed by patients switched from fluoxetine (44%), citalopram(42%), and paroxetine(42%). Escitalopram was well tolerated, with 6.6% discontinuation due to adverse events.

Conclusion: These data confirm that escitalopram can be effective in patients failing therapy with citalopram and other SSRIs. Patients who fail treatment with sertraline showed numerically better remission rates than patients failiog treatment with other SSRIs.

P02.165 ESCITALOPRAM IMPROVES SOMATIC SYMPTOMS OF DEPRESSION

M.H. Rapaport[1], A. Bose[2], K.G. Saikali[2]. [1]*Cedars-Sinai Medical Center, USA;* [2]*Forest Laboratories, USA*

Statement of the study: Somatic symptoms are commonly associated with depression. Escitalopram has been shown to improve a wide spectrum of symptoms associated with depression and anxiety disorders. We hypothesized that escitalopram would similarly improve somatic symptoms in depressed patients.

Methods: Two 8-week, randomized, placebo-controlled trials of escitalopram 10–20mg/day that utilized the Hamilton Depression Rating Scale (HAMD) have been performed in patients with moderate-to-severe depression (mean baseline HAMD = 25). The design of these trials was similar, and data from these trials were pooled. Somatic symptoms were measured by the HAMD Item 13 (Somatic Symptoms – General). LOCF results are presented.

Summary of results: Escitalopram treatment (N=365) led to significantly greater improvement in HAMD Item 13 scores than placebo treatment (N=244; –0.635 vs. –0.495; p<0.05). In the overall patient population, the mean change in HAMD total score from baseline to week 8 was statistically significant for escitalopram versus placebo, consistent with previously published results. In patients with clear-cut somatic complaints, defined as HAMD Item 13 score of 2(N=393), mean change from baseline in HAMD total score from baseline to week 8 was significantly greater for escitalopram than placebo (–11.397 vs. –9.010; p<0.05).

Conclusion: Escitalopram significantly improves somatic symptoms of depression, and is an effective antidepressant in depressed patients with somatic complaints.

P02.166 PATIENTS WITH SEVERE DEPRESSION: EFFICACY OF ESCITALOPRAM VS CITALOPRAM

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Statement of the study: This pooled analysis of data from three clinical trials compared the efficacy of escitalopram versus citalopram in a patient subpopulation with severe depression.

Methods: All trials were double-blinded with three arms (escitalopram, citalopram as active-reference drug, and placebo) and allowed the maximum escitalopram dose (20mg). A total of 506 severely depressed (Montgomery-Åsberg Depression Rating Scale [MADRS] ≥30) patients were included: escitalopram (N=169), citalopram (N=171), placebo (N=166).

Summary of results: The primary efficacy endpoint, mean change from baseline to endpoint (week 8) in the MADRS total score, was significantly higher for escitalopram- versus citalopram-treated patients (p=0.003; last-observation-carried-forward method). A significant difference from baseline in MADRS total score in favour of escitalopram versus citalopram was observed as early as Week 1 (p=0.01). There was a significant difference in response (≥50% decrease in baseline MADRS score) between escitalopram and citalopram (56% vs. 41%, respectively; p=0.007). A borderline significant difference was also observed for remission (MADRS≤12) rates (43% vs. 33% respectively, p=0.07, observed case method). Results from analyses of three secondary endpoints, change from baseline for the Hamilton rating scale for depression (HAM-D), Clinical global impression of improvement and severity scales (CGI-I and CGI-S), consistently supported the primary results.

Conclusion: The benefits of escitalopram versus citalopram were demonstrated both in terms of magnitude of clinical effect and time of onset of action.